DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on May 5, 2009 has been entered.

The Examiner acknowledges the applicant's remarks of May 5, 2009 made to the office action filed January 8, 2009. Claims 1-3, 6, 7, 9, 10, 14-17, 19, 27, 28 and 32 are pending. Claims 4, 5, 8, 9, 11-13, 18, 20-26, 29-31 and 33 are canceled. Claims 10, 14, 15, 17 and 19 are withdrawn. Claims 1-3, 6, 7 and 16 are amended.

In light of the cancellation of claims the 35 U.S.C. 103(a) rejection of claims 29, 30, 31 and 33 as being unpatentable over Bear et al. in view of Adam et al. is withdrawn.

For the reasons in the previous office action and below, the Applicant's arguments of the following 35 U.S.C. 103(a) rejections were found not persuasive, thus the rejection is upheld: 1) claims 1-8, 16, 20, 21 and 29 as being unpatentable over Adam et al. in view of Corsi et al. or Chimulera et al.; and 2) claims 9, 22, 27, 28, 32 and 33 as being unpatentable over Chiamulera et al. in view of Adam et al. as applied to claims 1-8, 16, 18, 20, 21 and 29 above. Both rejections are modified in light of the cancelled and amended claims.

Due to the amendments to the claims the modified 35 U.S.C. 103(a) rejections are made below. Applicant's arguments are addressed below. An interview summary of the interview with Attorney Wang on June 11, 2009 is attached.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

(1) Claims 1-3, 6, 7 and 16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Adam et al. (US 6407,094 B1) in view of Corsi et al. (US 2003/0195139 A1) or Chiamulera et al. (Nature Neuroscience, 2001, vol. 4(9), pp. 873-874).

Adam et al. teaches compounds that act as Group II (i.e. mGluR 2 and 3) metaboltropic glutamate receptor antagonist (see column 16, lines 47 and 48) and treat conditions which lead to glutamate-deficiency functions such as nicotine addiction, and opiate addiction (see column 1, lines 54-56 and column 3, lines 20-24; addresses claims 1-3, 6, 7 and 16). The antagonist can be in their pharmaceutically acceptable salts (see column 3, line 4).

Adam et al. does not teach an antagonist which modulated metabotropic glutamate receptor 5, or its administration in combination with the antagonist of Adam et al.

Corsi et al. teaches a method of treating substance dependence, wherein the substance is nicotine, opiate, cocaine, amphetamine, benzodiazepine and ethanol, comprising administering a therapeutically effective amount of an antagonist of mGluR5 (see claims 21-23; addresses claims 1-3, 6, 7 and 16). The compounds can be in the form of salts (see page 3, paragraph 55, lines 1 and 2).

Chiamulera et al. teaches the significant contribution of mGlu5 receptors to the behavioral effects of cocaine addiction (see page 873, column 1, paragraph 1, last 4 lines). A decrease of self-administration of cocaine was observed with an administration of the mGluR5 antagonist 2-methyl-6-(phenylethynyl)-pyridine (MPEP); see page 873, column 2, last paragraph, lines 1-4).

To one of ordinary skill in the art at the time of the invention would have found it obvious and motivated to combine the method of Adam et al. and a combination with an antagonist which modulates metabotropic glutamate receptor 5 because of the following: (1) Adam et al., Corsi et al., and Chiamulera et al. teach methods that treat addictive disorders; (2) Adam et al. teaches the treatment of addictive disorders with a mGluR 2 and 3 antagonist; and (3) Corsi et al. and Chiamulera et al. teach the treatment of an addictive disorder with a mGluR 5 antagonist. One would be motivated to combine the two methods because although different compounds are used and

antagonize different mGluR's, they both treat addictive disorders. "It is *prima facie* obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose.... [T]he idea of combining them flows logically from their having been individually taught in the prior art." *In re Kerkhoven*, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980). See also *In re Crockett*, 279 F.2d 274, 126 USPQ 186 (CCPA 1960); *Ex parte Quadranti*, 25 USPQ2d 1071 (Bd. Pat. App. & Inter. 1992); and *In re Geiger*, 815 F.2d 686, 2 USPQ2d 1276 (Fed. Cir. 1987).

(2) Claims 9, 27, 28 and 32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chiamulera et al. (Nature Neuroscience, 2001, vol. 4(9), pp. 873-874) in view of Adam et al. (US 6,407,094 B1) as applied to claims 1-3, 6, 7 and 16 above and Applicant's admitted prior art (see specification page 14, paragraph 2, lines 1 and 2, and page 16, group II, line 1 and 4).

The teachings of Chiamulera et al. and Adam et al. all are as applied to claims 1-3, 6, 7 and 16 above.

Chiamulera et al. and Adam et al. do not teach the antagonist 2S-2-amino-2-(1S,2S-2carboxycyclopropane-1-yl)-3-(xanth-9-yl)propionic acid (LY341495; claims 9 and 28). Also, the administration comprising: (a) administering to a subject in need

thereof, an effective amount of at least one antagonist that modulates at least one of mGluR2, 3, and 5 (specifically LY341495 or/and MPEP) during a first time period, wherein the first time period is a time period wherein the subject expects to be in an environment wherein or exposed to stimuli in the presence of which, the subject habitually uses an addictive substance; and (b) administering at least one antagonist that modulates at least one of mGluR2 and/or 3 (specifically LY341495) during a second time period, wherein the second time period is a time period wherein the subject is suffering from withdrawal and/or depression, is not taught (claim 27). Lastly, wherein the first antagonist and the second antagonist are administered to the subject sequentially or simultaneously is also not taught (claim 32)

To one of ordinary skill in the art at the time of the invention would have found it obvious and motivated to combine the method of Chiamulera et al. and the antagonist LY341495 because of the following: (1) both Chiamulera et. al. and Adam et al. teach methods to treat substance abuse; (2) Adam et al. teaches the treatment of an addictive disorders or depression with a mGluR 2 and 3 antagonist; and (3) LY341495 is a well known mGluR 2 and 3 antagonist in the art (indicated by the specification page 14, paragraph 2, lines 1 and 2, and page 16, group II, line 1 and 4). One would be motivated to combine the two methods because although different compounds are used and antagonize different mGluR's, they both treat substance abuse. "It is *prima facie* obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very

same purpose.... [T]he idea of combining them flows logically from their having been individually taught in the prior art." *In re Kerkhoven*, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980). See also *In re Crockett*, 279 F.2d 274, 126 USPQ 186 (CCPA 1960); *Ex parte Quadranti*, 25 USPQ2d 1071 (Bd. Pat. App. & Inter. 1992); and *In re Geiger*, 815 F.2d 686, 2 USPQ2d 1276 (Fed. Cir. 1987).

To one of ordinary skill in the art at the time of the invention would have found it obvious and motivated to combine the method of Chiamulera et al. and an administration comprising: (a) administering to a subject in need thereof, an effective amount of at least one antagonist that modulates at least one of mGluR2, 3, and 5 (specifically LY341495 or/and MPEP) during a first time period, wherein the first time period is a time period wherein the subject expects to be in an environment wherein or exposed to stimuli in the presence of which, the subject habitually uses an addictive substance; and (b) administering at least one antagonist that modulates at least one of mGluR2 and/or 3 (specifically LY341495) during a second time period, wherein the second time period is a time period wherein the subject is suffering from withdrawal and/or depression; or (c) wherein the first antagonist and the second antagonist are administered to the subject sequentially or simultaneously because without unexpected results, one skilled in the art can reasonably design the period of administration.

Response to Arguments

> The Applicant argues that the Examiner maintained the assertion that the prior art taught that non-selective mGluR antagonist MCPG was effective in treating withdrawal symptoms. The Applicant's clarify that Fundytus et al. reports that chronic administration of MCPG prevented the development of morphine dependence in normal rats which were simultaneously administered with morphine and the antagonist (Figure 1). Further rats already with induced morphine dependence, acute administration of MCPG did not lead to improved withdrawal symptoms relative to controls (Figure 2). Figure 1, in which the Examiner depends on is merely intended as an indicator of whether dependence was developed or prevented in rats receiving the different combination of drugs. On the contrary, Fundytus et al. results show a preventative effect of the antagonist, and no efficacy in treating withdrawal if the antagonist is administered after the development of dependence. Thus, the reference teaches away from combining mGluR2/3 antagonist and a mGluR5 antagonist as presently claimed.

The Examiner disagrees because first and the most important, **Fundytus et al. is not used as a reference to reject the claims**. The current claims are rejected as being unpatentable over Adam et al., Chiamulera et al. and Corsi et al. The remarks in the previous office action and below in regards to Fundytus et al. are simply to addresses Applicant's arguments. **Again, the Examiner does not rely on Fundytus et al. to teach the applicant's invention.** In regards to Fundytus et al. teaching away from the present invention, the Examiner disagrees because Fundytus et al. provides a means of attenuating withdrawal symptoms (i.e. reducing withdrawal symptoms) by administering the non-selective antagonist MCPG (see page 1018, column 2, discussion, lines 1-6; and page 1017, column 1, paragraph 3 in its entirety, Figure 1b).

Thus, the non-selective mGluR antagonist MCCG (at receptors 1, 2, 3, and 5) was effective in treating withdrawal symptoms.

> The Applicant further argues that the date noted by the Examiner in Mills et al. do not teach or suggest a combination of two antagonists of two different mGluRs, let alone showing that such a combination would be effective in treating withdrawal symptoms. Thus, the reference to Mills et al. by the Examiner by no means negate that fact that mGluR2/3 antagonists and mGluR5 antagonists can have opposing neurochemical effects on glutamate neurotransmission, and therefore would not be obvious to combine. Similarly, Applicants are puzzled by the Examiner's statements for the data presented in Xi et al. The Applicant disagrees with the *In re Kerkhoven* rationale because of the opposing activities of mGluR5 and mGluR2/3 antagonists and the existence of abundant evidence indicating undesirablility of potential side effects of such a combination.

The Examiner disagrees because although different Groups have opposite results in regards to the increasing or decreasing the amount of glutamate transmission, the claimed compounds both treat substance abuse. One can not assume that the two Groups would automatically cancel each other's activity and be non-effective. The data presented in the previous office action for Mills et al. was to point out that the amount of glutamate can be adjusted by adding different Group antagonist. The data presented in the previous action by Xi et al. was to demonstrate that the amount of glutamate can be adjusted by adding different receptor agonist and/or antagonist. Particularly, if one follows the Applicant's arguments that the two antagonists would not be effective, one would expect that when a mGluR2/3 agonist is added to a mGluR2/3 antagonist the activities would be cancelled out by its opposing activities. In contrast, Xi et al. shows that by adding the agonist to the antagonist the glutamate was decreased (see Figure

2b and page 164, column 1, paragraph 4, lines 1-8). Therefore, it is not concrete that by adding a mGluR2/3 and a mGluR5 antagonist that the activities would cancel each other out or be non-effective. As stated above, both Groups and the claimed compounds have been shown to effectively treat substance abuse, and thus provides motivation to combine the two compounds to treat substance abuse. The claims are drawn to treating addiction not the mechanism in which it happens. The Examiner's reasons for combining the references do not need to be the same as the Applicant's. The Examiner suggest that the Applicant's show unexpected results such as synergy of the two compounds to treat substance addictions claimed over the independent compounds.

Conclusion

No claims allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to KENDRA D. CARTER whose telephone number is (571)272-9034. The examiner can normally be reached on 7:30 am - 4:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan can be reached on (571) 272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/K. D. C./

Examiner, Art Unit 1617

/SREENI PADMANABHAN/
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